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Lara Phillips

Thomas Jefferson University, Lara.Phillips@jefferson.edu

Buddha Basnyat

Oxford University Clinical Research Unit - Nepal

Yuchiao Chang

Harvard Medical School

Erik R. Swenson

University of Washington

N. Stuart Harris

Harvard Medical School

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Findings of cognitive impairment at high altitude: relationships to
acetazolamide use and acute mountain sickness

Lara Phillips, MD^{1,2}, Buddha Basnyat MD³, Yuchiao Chang PhD¹, Erik R. Swenson MD⁴
and N. Stuart Harris MD MFA ¹

¹Division of Wilderness Medicine, Department of Emergency Medicine, Massachusetts
General Hospital, Harvard Medical School, Boston, MA 02114, USA.

²Department of Emergency Medicine, Thomas Jefferson University Hospital,
Philadelphia, PA 19107, USA.

³Oxford University Clinical Research Unit - Nepal; Himalayan Rescue Association,
Kathmandu, Nepal.

⁴ Medical Service, Veterans Affairs Puget Sound Health Care System, University of
Washington, Seattle, WA 98108, USA.

1 **Abstract**

2 **Objective:** Acute mountain sickness (AMS) is defined by patient-reported symptoms
3 using the Lake Louise Score (LLS), which does not necessarily provide insight into
4 possible central nervous system (CNS) dysfunction. Our hypothesis was that AMS might
5 be associated with cognitive impairment (CI) and may go undetected unless a sensitive
6 test is applied. A standardized test for mild CI could provide a potential new tool to better
7 characterize altitude-related CNS dysfunction.

8 **Methods:** We compared a cognitive screening tool with the LLS. We recruited adult
9 native English-speaking subjects visiting Himalayan Rescue Association aid posts in
10 Nepal at 3520m (11,550ft) and 4550m (14,930ft). Subjects were administered the LLS
11 and a slightly modified version of the Quick Mild Cognitive Impairment Screen (eQmci).
12 Medication use for altitude illness was recorded. LLS and eQmci scores were compared
13 using the Spearman correlation coefficient. A cut-off of ≥ 3 with at least 1 point for
14 headache was used for the LLS to diagnose AMS and 67 or less for the eQmci to
15 diagnose CI. Data also included medication use.

16 **Results:** Seventy-nine subjects were enrolled. Twenty-two (28%) subjects met criteria for
17 AMS and 17 (22%) subjects met criteria for CI. There was a weak correlation ($r^2=0.06$,
18 $p=0.04$) between eQmci score and LLS. In matched subjects with identical LLS, recent
19 acetazolamide use was significantly associated with more frequent CI.

20 **Conclusion:** Field assessment of CI using a rapid standardized tool demonstrated a
21 substantial number of subjects had mild CI following rapid ascent to 3520-4550m
22 (11,548-14,927ft). The weak correlation between the LLS and eQmci suggests that AMS

Acute Mountain Sickness and Cognition

1 is not associated with CI. Use of acetazolamide may have an association with CI at all
2 levels of AMS severity.

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1 **Introduction**

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3 Acute mountain sickness (AMS) commonly occurs following acute exposure to high
4 altitude (> 2,500m or 8200 ft) (Hackett & Roach, 2012; Wilson & Imray, 2009). AMS is
5 defined by symptoms including headache, dizziness or lightheadedness, nausea and
6 vomiting, difficulty sleeping, and fatigue. The Lake Louise self-reported score (LLS) is
7 one of the most widely used diagnostic scoring systems to diagnose AMS (Roach et al.,
8 1993).

9

10 Previous work has suggested the possibility of cognitive impairment (CI) in AMS. While
11 it is known high altitude conditions can impair cognition, and alter executive, memory
12 and language processes (Asmaro et al., 2013; Du et al., 1999; Kramer et al., 1993; Li et
13 al., 2000; McCarthy et al., 1995; Petrassi et al., 2012; Turner et al., 2015; Virues-Ortega
14 et al., 2004; Wu et al., 1998), it is generally accepted that altitude-related CI occurs
15 independently of AMS (Kramer et al., 1993; Virues-Ortega et al., 2004). However, some
16 studies do suggest CI and AMS are associated (Bian et al., 2015; Forster, 1985; Regard et
17 al., 1991, Shukitt-Hale et al., 1991, Issa et al., 2016). AMS is a symptom complex that
18 may be due to early, mild cerebral edema and increased intracranial pressure (Lawley et
19 al., 2016; Sagoo et al., 2016). Cerebral manifestations of acute altitude illness span from
20 common, benign AMS to potentially fatal high altitude cerebral edema (HACE). AMS
21 has no obvious neurologic signs (e.g., ataxia), but these are found in HACE. Because
22 high altitude cerebral illnesses appear to be a continuum from the mild symptoms of
23 AMS to severe symptoms with overt CNS findings of HACE, our hypothesis was that a

sensitive objective test for high altitude-related mild CI using an easily available field technique would correlate closely with the presence and severity of AMS.

The Quick Mild Cognitive Impairment (Qmci) screen has potential to detect mild CI in the field at high altitude. The Qmci screen rapidly and reliably detects early mild CI (Molloy et al., 2005; O'Caoimh et al., 2012). We tested a slightly modified version of the Qmci (which we refer to as the Environmental Quick Mild Cognitive Impairment Screen (eQmci)) and sought to determine if AMS is associated with CI. We compared the eQmci to the LLS and screened for medication by use of drugs for prophylaxis of AMS.

Methods

Study Population

All of our subjects had recently and rapidly ascended by vehicle and foot to the two testing sites in the Annapurna region of the Nepalese Himalayas. Adult native English speaking subjects visiting the Himalayan Rescue Association aid post in Manang at 3520 m (11,550 ft) or at a temporary aid post in Thorong Phedi at 4550 m (14,930 ft) were offered enrollment into the study. Surveys were only offered to clinically stable subjects at the end of their medical visit after clearance from the health professional caring for them. Inclusion criteria included native English-speaking adults between the ages of 18 and 65 years trekking through Manang or Thorong Phedi. This included asymptomatic subjects who presented themselves to the clinic for education and prevention of illness. Subjects were not excluded for having minor ailments including joint pain, blisters, rashes, diarrhea and cough. Exclusion criteria included a history of dementia and

recreational drug or alcohol use. All recruited subjects were trekkers who had ascended from 8000 ft (2440 m) within 1 week. No permanent residents of high altitude were recruited.

Study Procedures

Subjects who presented to the aid posts meeting criteria were enrolled. A consent document with information about the study was presented to each volunteer and written consent was obtained. Information collected from each subject included age, years of education, history of dementia, fluency in English, rate of ascent, medication use, and self-rated high altitude experience. Subjects were asked about prophylactic and treatment medications for high altitude illness, analgesics and any potentially sedating drugs during their trek through the Annapurna region. Medications for general medical problems (e.g. antihypertensives, oral contraceptives, thyroid replacement, etc.) were not recorded. Each subject enrolled was administered the LLS and eQmci by a single investigator. This study was approved (Protocol number 2014P001803) by the Partners Institutional Review Board (Boston, MA, USA) and Nepali Health Research Council.

Testing

The LLS uses a 5-item scale, which surveys a subject's assessment of headache, dizziness or lightheadedness, fatigue or weakness, gastrointestinal distress, and difficulty sleeping. Each symptom is graded on a scale of 0 (not present) to 3 (severe). The presence of a headache (score at least one for headache) and a total score of greater than or equal to 3 is required to diagnose AMS (Roach et al., 1993).

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2 The Qmci consists of 6 subtests including orientation, registration, clock drawing,
3 delayed recall, verbal fluency and logical memory. It has a median administration time of
4 4.24 minutes (O'Caoimh et al., 2013). The range of score is 0 to 100. Two modifications
5 were made to better apply this screen in high altitude wilderness settings. We removed
6 the clock drawing task given the practical concern of needing to remove gloves to
7 perform the test in a very cold environment. The clock drawing test is useful to assess
8 visuospatial cognition, but is clinically a less useful subtest when compared to other
9 elements in the Qmci (O'Caoimh et al., 2013). Instead, in order to maintain a distracting
10 task before the verbal recall exam, subjects were asked to count backwards from 100 by
11 sevens. A second modification was made in which proper names replaced common
12 names for repetition and recall testing. Proper names were matched for frequency of
13 occurrence in the English language. High altitude seems to have a more dramatic effect
14 on the recall of proper names while recall of common names is relatively resistant to
15 hypoxia (Pelamatti et al., 2003). The remaining subtests were unchanged. Subjects with
16 normal cognition have a median score of 75 (O'Caoimh R, 2014). Subjects who score \leq
17 67 out of 100 meet criteria for mild CI and those who score \leq 53 out of 100 meet criteria
18 for dementia (O'Caoimh R, 2014).

19

20 *Statistical Analysis*

21 Continuous variables were compared using two-sample t-tests while categorical variables
22 were measured using frequency and percentage and compared using chi-square tests. The
23 relationship between the two measures was summarized using a Spearman correlation

coefficient. Two-sided p values ≤ 0.05 were considered as statistically significant. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Seventy-nine subjects were enrolled in the study. All subjects who enrolled completed the surveys. Twenty-two subjects (28 %) met criteria for AMS and 17 subjects (22 %) met criteria for mild CI.

Table I presents demographic subject information stratified by presence of AMS and CI. We found a significant difference in recent acetazolamide use between groups with and without AMS. Twenty-three out of 79 (29 %) took acetazolamide in the last 24 hours. Of these subjects, 10 (43 %) had AMS and 11 (48 %) had CI. A higher percentage of subjects diagnosed with AMS had taken acetazolamide in the previous 24 hours compared to those without AMS (45 % vs. 23 %, $p = 0.047$). Similarly, a higher percentage of subjects with CI had taken acetazolamide in the last 24 hours compared to those without CI (65 % vs. 19 %, $p = 0.0003$). Subjects with CI were slightly older (37 ± 14 vs. 29 ± 9 , $p = 0.058$) and there were no other significant differences in group characteristics [e.g. age, sex, nationality, education, days above 8000 ft, self-rated experience at high altitude, and paracetamol and non-steroidal anti-inflammatory (NSAID) use] in subjects with and without AMS, or with and without CI.

As this study tested subjects at two different altitudes, we also analyzed the results from only Manang, where the majority of subjects were recruited ($n = 62$). When subjects from

1 Thorong Phedi were excluded, there was still a significant difference in recent
2 acetazolamide use between groups with and without AMS. Specifically, a higher
3 percentage of subjects diagnosed with AMS had taken acetazolamide in the last 24 hours
4 compared to those without AMS (44 % vs. 13 %, $p = 0.009$). Similarly, a higher
5 percentage of subjects with CI had taken acetazolamide in the last 24 hours compared to
6 those without CI (54 % vs. 12 %, $p = 0.001$). There were no other significant differences
7 in group characteristics.

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9 There was a very weak correlation between the eQmci score and LLS based on the
10 Spearman correlation coefficient ($r = -0.24$, $p = 0.04$) as only 5% of the variance in the
11 eQmci can be attributed to LLS (see Figure 1). Among the 79 subjects, 6 (8 %) tested
12 positive for both AMS and CI and 46 (58 %) tested negative for both. Sixteen subjects
13 (20 %) met the LLS criteria for AMS but had no CI. The remaining 11 subjects (14 %) were
14 cognitively impaired but did not have AMS. Those with concordance between the
15 eQmci and LLS were more likely to be male (69 % vs. 41 %, $p = 0.014$) and there was no
16 other significant difference in subject demographic characteristics between those with
17 and without concordance between the eQmci and LLS.

18
19 Components of the LLS were also analyzed as presented in Table II. There was no strong
20 correlation between the eQmci score and any of the LLS components, including
21 headache. The strongest correlation was seen in gastrointestinal symptoms, which was
22 still relatively weak ($r = -0.28$, $p = 0.011$).

We conducted a further analysis to examine the effect of acetazolamide on eQmci score. Figure 2 shows the distribution of eQmci from those subjects with and without acetazolamide use in the last 24 hours. The overall mean eQmci scores were lower in subjects who took acetazolamide (69 vs. 77, $p = 0.0007$). The finding was consistent when limited to subjects with the same LLS score. Table III compares the prevalence of CI from subjects with and without acetazolamide use in the last 24 hours. Overall, CI were more common among subjects with acetazolamide use (47.8% vs. 10.7 %, $p = 0.0006$). When stratified by AMS status, the finding remained consistent. Among those without AMS, CI was significantly more frequent in subjects who took acetazolamide than in subjects who had not taken the drug (46.2 % vs. 11.4 %, $p = 0.011$). Similarly, among subjects with AMS, those who took acetazolamide showed a trend to have more CI (50.0 % vs. 8.3 %, $p = 0.056$) than those who had not taken the drug.

Discussion

Acute ascent to high altitude can impair CNS function including short-term memory, working memory, and executive functioning (Asmaro et al., 2013; de Aquino Lemos et al., 2012; Hornbein et al., 1989; Kennedy et al., 1989; Kramer et al., 1993; Petiet et al., 1988; Petrassi et al., 2012; Shukitt-Hale et al., 1994; Turner et al., 2015; Virues-Ortega et al., 2004). We hypothesized that a field test for mild CI would provide an objective measure of altitude-related CNS dysfunction which would correlate with the presence and severity of AMS. Our results do not suggest a significant correlation between the eQmci and LLS to support this hypothesis.

Lack of relationship between cognitive impairment and acute mountain sickness

The lack of correlation between the LLS and eQmci suggests that CI occurs independently of AMS. This is consistent with previous research (Virues-Ortega et al., 2004). Krammer et al. (1993) tested twenty climbers at 4360 m (14,304 ft) ascending Denali. While they demonstrated deficits in learning and retention in perceptual and memory tasks, they did not correlate with AMS. In one study that tested mental capacity, subjects with AMS were worse in pursuit aiming compared to subjects without AMS, but in the remaining battery of cognitive tests, no significant differences were found (Bian et al., 2015). It is possible that there is a difference in the aspects of cognitive deficits seen with and without AMS. In the study by Regard et al. (1991), subjects simulated ascent to 4500 m (14,734 ft) over 24 hours in a hypobaric chamber. Those with AMS had deficiencies in short-term memory, but improved in conceptual tasks while those without AMS had improved short-term memory, but no improvement in conceptual tasks (Regard et al., 1991).

The lack of any relationship in our study and in others between CI and AMS, both of which are inextricably linked to the hypoxemia of high altitude and are largely neurological in their expression, is somewhat counterintuitive. However, hypoxemia can very rapidly lead to cognitive deficits (usually without symptoms) in a span of minutes even in healthy persons, whereas AMS develops more slowly and generally is not evident for many hours. Furthermore, people differ widely in the risk for AMS as a result of varying sensitivity to hypoxemia involving pathways not fully understood, but possibly related to trigeminal nerve sensitivity and/or very mild brain swelling that may not

necessarily impair neuronal functioning. Thus CI at high altitude and AMS likely have different pathophysiological bases, but may coexist in some people on any occasion.

Cognitive impairment at altitude

Our study found a surprisingly high prevalence of CI: 17 subjects (22 %) met criteria for mild CI. In subjects with an age range similar to that in our study, no subject tested at sea-level was found to have CI (Molloy, 2015). An incidental finding of our study was that acetazolamide use, independent of the severity of AMS was associated with CI at high altitude.

The discriminating power of the Qmci for detecting CI is influenced by age; specifically it is less accurate for subjects older than 75 years (O’Caoimh, 2014). The cut-off of 67 used in this study is recommended for younger adults (≤ 75 years) with more education (\geq high school). All subjects in our study were in this category. At this cut-off the Qmci has 86 % sensitivity and 89 % specificity for detecting the presence of mild CI. CI is not seen in a young healthy educated population (Molloy, 2015). Sex does not significantly affect cut-off scores (O’Caoimh R, 2014).

Acetazolamide and cognitive impairment

In subjects taking acetazolamide, we found a high incidence of both AMS and of CI. Acetazolamide has been associated with confusion (Swenson, 2014). In a randomized study of subjects at high altitude, subjects who received prophylactic acetazolamide (125 mg twice per day) had impaired neuropsychological measures of concentration, cognitive

processing speed, reaction time, short-term memory, and working memory (Wang et al., 2013). In a similar study, subjects who took acetazolamide (500 mg slow release, once per day) actually showed improvement in certain psychological tests (White, 1984). In addition to higher daily acetazolamide dosing, this second study differed from the former in that subjects traveled on foot rather than being airlifted to a higher altitude which may be a confounding factor. A more recent study found that at sea level, acetazolamide use is associated in a dose-dependent fashion with a spectrum of psychometric impairments, including poor concentration, imbalance and slower reaction time responses (Collier, 2016). Our study did not differentiate between prophylactic or treatment doses, but a future study can be designed to match groups with regard to this variable. Physiologically, acetazolamide functions as a carbonic anhydrase (CA) inhibitor. CA plays a role in signal processing, synaptic plasticity, memory, nerve conduction and cerebral oxygenation and consumption (Brechue et al., 1997; Sun & Alkon, 2002; Wang et al., 2015). CA inhibition is likely responsible for the deficits in cognition. Whether CI arises from the drug-induced metabolic acidosis that partially compensates for the magnitude of the respiratory alkalosis (hypocapnia) or from more direct effects in the CNS is not easily resolved, but a combination of the two may be likely. At sea level only 50 % of patients taking acetazolamide (250 mg, four times a day) have relief of common CNS side effects with concurrent bicarbonate supplementation sufficient to correct the metabolic acidosis (Lichter, 1981).

Limitations of the study

1 There are several limitations in this investigation. First, we made modifications to the
2 eQmci (the clock drawing task was replaced by reciting serial sevens and the repetition
3 and recall of names were changed from common to proper). Though the Qmci has been
4 validated against the Montreal Cognitive Assessment and Standardized Mini-Mental
5 State Exam, the two minor changes in the eQmci were not validated prior to testing. This
6 potentially could have an effect on the cut-off values originally tested for the Qmci.
7 Second, traveling to a distant, culturally unfamiliar location may alter one's performance
8 on a cognitive test. Third, there was a relatively small sample size. Other trends may be
9 been seen with a more robust sample. Unfortunately, our recruitment was limited as a
10 result of the devastating 2015 earthquake in Nepal, which resulted in premature
11 termination. Fourth, there may be several secondary influences on neuropsychological
12 function including fatigue, hypothermia, desynchronosis, upper respiratory infections,
13 and exposure to a new environment. An individual diagnosis was not recorded for every
14 patient. However, most presentations to the clinic that were unrelated to altitude were
15 quite minor (e.g. blisters) and would not be expected to affect cognitive function. Fifth,
16 there was no low-altitude control group, nor were our subjects tested at low altitude to
17 examine baseline scores. Sixth, there were no measurements of arterial oxygenation
18 saturation by pulse oximetry. In future studies, this would be a better indicator of cerebral
19 hypoxic stress than the actual altitude. Seventh, there were no longitudinal data to
20 determine if low eQmci scores correlate with the development of HACE. Defining the
21 clinical significance of mild CI and determining whether it can be used to predict those
22 that will develop HACE or experience other clinical relevant sequelae are areas of future
23 research. In addition, there were no longitudinal data on the discontinuation of

1 acetazolamide. Eighth, subjects were studied at two different altitudes. However, the
2 results were not significantly changed when the data were limited to Manang, where most
3 subjects were tested. Ninth, in a convenience sample, in which subject self-selection
4 exists (researchers have no control or insight in subjects' decisions to continue to ascend
5 or not), unmeasured confounding variables may exist that could reduce the validity of our
6 conclusions.

8 *Future Studies*

9 Regardless of AMS, screening of mild CI may be useful for early detection of impaired
10 cognition and poor decisional judgment at high altitude. Our study, however, does not
11 demonstrate any clinical significance of having mild CI diagnosed by a cognitive
12 function test, since we did not measure rates of adverse health events or poor decision-
13 making, but this is a potential area of future research. Cognitive tests are sensitive and
14 have the potential to screen for hypoxic impairment at early stages before subjects
15 develop symptoms or demonstrate poor judgment (Stepanek et al., 2013). Other cognitive
16 tests have been employed at high altitude such as clock drawing (Quigley & Zafren,
17 2016). The eQmci can be administered in less than five minutes, does not require any
18 special equipment, and has multiple versions available to minimize a learning effect
19 when administered to the same subject over different points in time (Cunje et al., 2007).
20 Future longitudinal studies in trekkers, as well as validation of the eQmci and comparison
21 to other cognitive tests, may be useful to investigate the clinical relevance of mild CI.
22 Further study of secondary influences on CI at high altitude (e.g. exercise, medications,
23 sleep quality) are also needed. Lastly, the comparison of CI with other objective

measures (e.g., optic nerve sheath diameter, ultrasonography, cerebral magnetic resonance imaging, serum biomarkers) might help advance a better understanding of acute altitude-related CNS disease.

In summary, our data demonstrate only a weak correlation between the LLS and eQmci, but a surprising prevalence of CI, an objective measure of CNS dysfunction, at high altitude. CI was prevalent in subjects both with and without AMS. The presence of CI in otherwise asymptomatic trekkers raises concerns for unrecognized CI at altitude. Furthermore, we found that acetazolamide use, independent of the severity of AMS was associated with CI at high altitude. Further research using CI testing may help define objective measures of CNS dysfunction at altitude.

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Table and Figure Legend

Table I: Basic demographics. Percentages are reported with respect to different subgroups (LLS < 3 , LLS ≥ 3 , eQmci > 67 , eQmci ≤ 67).

Table II: Analysis of components of the LLS Associated with the eQmci score is demonstrated with relatively weak correlation.

Table III: The relationship between eQmci scores and acetazolamide use were analyzed. The overall mean eQmci scores were significantly lower in subjects that took acetazolamide.

Figure 1: A scatter plot was created between LLS and eQmci scores. There was poor correlation between the eQmci score and the LLS based on the Spearman (-0.24) correlation coefficients.

Figure 2: A graphic display of the range of values for the eQmci in subjects with and without acetazolamide use in the last 24 hours. eQmci scores were lower in subjects who took acetazolamide ($p < 0.001$).

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